



Allergen-specific immunotherapy and risk of autoimmune disease

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Purpose of review

After 100 years of experience with allergen-specific immunotherapy (SIT), an issue that is still unresolved is whether SIT can act as a trigger of, or as a risk factor for, autoimmune disease. We searched the literature for evidence on this topic.

Recent findings

Several case reports of autoimmune disease development with plausible relation to SIT have been published. Vasculitis reactions accounted for the majority of case reports retrieved in our literature search. Whether the number of reported cases is higher or lower than what would be expected by chance is not possible to determine from existing data. There are no published data on autoimmune disease development in patients participating in randomized trials of the effects of SIT. One nonrandomized pharmacoepidemiological study did not detect an increased risk of autoimmune disease development during SIT as compared with the risk during conventional allergy treatment.

Summary

In conclusion, development of autoimmune disease in allergic patients treated with SIT is rare. Nevertheless, as a principle of caution, it seems reasonable to carefully evaluate the indication for SIT, that is, risks versus benefits, in patients with established autoimmune disease or a strong family history of autoimmune disease.

Keywords

allergen-specific immunotherapy, autoimmune disease, side-effects

INTRODUCTION

After 100 years of experience with allergen-specific immunotherapy (SIT), an issue that is still unresolved is whether SIT can act as a trigger of, or as a risk factor for, autoimmune disease. According to the T helper type 1 (Th1)/Th2 paradigm, the immune response of allergic patients is skewed toward a Th2 lymphocyte-dominated immune response; whereas the immune response of patients with autoimmune disease is skewed toward Th1 lymphocyte-dominated immune response. Along this line, one would expect allergic diseases to be inversely related to autoimmune disease, that is, autoimmune disease being less common in persons with allergies and vice versa. However, evidence to support this has not been consistent and the Th1/Th2 paradigm is considered to be a too simplistic view on the immunological and pathological mechanisms involved in these diseases. SIT is a well documented treatment of immunoglobulin E (IgE) mediated allergies, targeting the cause of allergy by suppressing the IgE-mediated immune response

favoring tolerance to the offending allergens. SIT suppresses the Th2 response to allergens, which has led to concern that SIT could enhance Th1 responses and risk of autoimmune disease. Over the years, cases of autoimmune disease, such as Sjögren's syndrome [1], multiple sclerosis [2], localized scleroderma [3], recurrent pericarditis [4], and vasculitis [5], have been reported during the course of SIT (reviewed in the following). As a consequence and principle of caution, some international guidelines consider autoimmune disease a relative contraindication for SIT [6], whereas others recommend an

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KEY POINTS

- Evidence to support the idea that SIT can act as a trigger of autoimmune diseases is weak and mainly based on case reports.
- Vasculitis reactions accounted for the majority of case reports retrieved in our literature search.
- The risk of autoimmune disease in patients receiving SIT is very low.
- On the basis of current evidence, it has not been possible to determine whether the risk of autoimmune disease is higher or lower in patients receiving SIT than in patients receiving other types of allergy treatment.

individual evaluation of the patient [7[°]]. The aim of the present review is to summarize the clinical evidence, for example, from trials, epidemiological studies, and case reports, to support or refute the notion that SIT can act as a trigger of, or a risk factor for, autoimmune diseases. We searched the *PubMed*, *Embase*, *Web of Science*, and *Cochrane Library* for relevant articles. We used the following search terms: ['immunotherapy' AND ('allergen' OR 'allergy')] AND 'autoimmune disease'. Furthermore, 'autoimmune disease' was also replaced by each specific disease from a list of 20 autoimmune diseases (e.g., sarcoidosis, pericarditis, and sclerosis).

EVIDENCE FROM CONTROLLED STUDIES

The randomized, placebo-controlled clinical trial is the gold standard (or the least biased study design) for the assessment of possible beneficial and adverse effects of interventions in humans. To the best of our knowledge, there are no published data from randomized trials of SIT reporting the risk of autoimmune diseases. There may be several reasons for this. First, the incidence of autoimmune disease is so rare that no randomized trial to date has had sufficient size (power) and length of follow-up to properly estimate the effect of SIT on the risk of autoimmune disease. Second, as autoimmune disease has not been an a priori outcome of any study, available data on autoimmune disease occurring during trials of SIT may have had low priority for publication.

A pharmacoepidemiologic approach taking advantage of linkage between nationwide registries for medications and diseases, thereby obtaining complete follow-up of large populations may provide the opportunity to study hitherto unrecognized rare adverse or beneficial effects of medications. To our knowledge, only one pharmacoepidemiological study has tried to assess the association between SIT

and incidence of autoimmune disease. The study used all Danish citizens as the study base and took advantage of the unique Danish registries on health-care data including use of medication [8[°]]. The prospectively assessed incidence (the proportion of novel cases among unaffected individuals) of autoimmune disease among individuals receiving SIT was compared with the incidence of autoimmune disease among individuals receiving conventional allergy treatment (nasal steroids and oral antihistamines). A total of 206 (total of 122 914 person-years observed) and 6071 (2.378 545 person-years observed) cases of autoimmune disease were observed among persons receiving SIT and conventional allergy treatment, respectively. SIT as compared with conventional allergy treatment was associated with a slightly, but significantly lower relative risk of autoimmune disease (adjusted hazard ratio 0.86; 95% confidence interval 0.74–0.99) [8[°]]. This means that persons treated with SIT as compared with conventional allergy treatment had a 14% lower incidence of autoimmune disease. The effect was mainly seen during the first 6 months after initiation of SIT. However, nonrandomized studies may be more prone to confounding and bias than randomized studies, and it is difficult to be certain that treatment groups were completely comparable with regard to other determinants of autoimmune disease. On the contrary, the fact that a lower incidence was observed in individuals receiving SIT could favor the interpretation that SIT does not confer any major risk of developing autoimmune disease. However, it is important to recognize that the above risk estimate reflects the risk of autoimmune disease for the average patient and not a patient with a predisposition to autoimmune disease. Thus, we cannot rule out that patients with a strong genetic predisposition to autoimmune disease could respond very differently to SIT with regard to risk of autoimmune disease development.

EVIDENCE FROM CASE REPORTS

The results of our literature search for case (casuistic) reports of autoimmune disease with a possible relationship to SIT are summarized in Table 1 [1–5,9–18]. Some of the cases were observed after cessation of SIT, for example, the three reported cases of sarcoidosis [9] and their relationships with SIT seem less convincing. In contrast, in some cases, the relationship with SIT seems convincing due to the observation that SIT-related reactions were reproducible on repeated administration (see column with comments in Table 1). Vasculitis was the most commonly reported type of reaction in the case reports retrieved in our literature search.

Table 1. Published case reports of autoimmune disease or autoimmunity-like reactions with possible relationship to allergen-specific immunotherapy

Reference	Type of disease (number of cases)	Country/sex/age	Type of allergens (number of cases)	Comorbidities	Comments
El <i>et al.</i> [9]	Sarcoidosis (three)	Turkey/two men and one woman/18, 30, and 34 years	Mixture of allergens (two). Grass pollen (one)	Rhinitis and asthma	All cases occurred after end of SIT. Two of the cases occurred during stay in Sweden
Maciel and Morfin [3]	Scleroderma (one)	Mexico/woman/8 years	Sublingual IPI ASAC	Rhinitis, asthma, severe obesity	Grandmother died of systemic sclerosis
Turkcapar <i>et al.</i> [1]	Sjögren's syndrome (one)	Turkey/woman/25 years	Grass pollen	Rhinitis	
Quirce <i>et al.</i> [4]	Pericarditis (one)	Spain/woman/29 years	Mixture of allergens	Rhinitis	Two separate admissions with pericarditis 1 month apart. Both occurred within 24 h following injection of SIT
Taylor [5]	Vasculitis (one)	USA/male/59 years	Mixture of allergens	Rhinitis, hyperlipidemia	Exacerbation of rash on repeated injection
Phanuphak and Kohler [10]	Vasculitis (polyarteritis nodosa) (six)	USA/two women and four men/29–72 years	Mixture of allergens (six)	Rhinitis, asthma	
Karakay <i>et al.</i> [11]	Erythema multiforme (one)	Turkey/woman/25 years	Mixture of allergens	Rhinitis	
Chabane <i>et al.</i> [12]	Vasculitis/serum sickness (one)	France/two men/both 47 years	Mixture of insect venom (one) and inhalant allergens (one)	Insect venom allergy/asthma	Rush immunotherapy
Nakajima <i>et al.</i> [2]	Multiple sclerosis	Japan/woman/43 years	House dust mite and Japanese cedar	Rhinitis	The potential eliciting dose of SIT was given concomitantly with influenza vaccination
Sánchez-Morillas <i>et al.</i> [13]	Vasculitis (one)	Spain/woman/66 years	Cupressu arizonica pollen	Asthma	Reactions within 48 h following injections of SIT on two occasions 1 month apart
Berbis <i>et al.</i> [14]	Vasculitis (one)	France/?/?	Mixture of allergens	Asthma	
Cruz and Bahna [15]	Serum sickness (one)	USA/male/50 years	Mixture of allergens	Rhinitis	Symptoms followed injection of wrong vaccine
Branca-Ferreira <i>et al.</i> [16]	Digital vasculitis (one)	Portugal/Portuguese/43 years	<i>Dermatophagoides pteronyssinus</i>	Rhinitis, hypertension (treated with nifedipine)	Two similar reactions following injections 10 days apart
Cabrera <i>et al.</i> [17]	Digital vasculitis (one)	USA/male/37 years	Mixture of allergens	Rhinitis	Symptoms occurred 2 months after discontinuation of SIT due to anaphylactic reactions
Shabrawi-Caelen, 2009 [18]	Dermal sclerosis of arm/shoulder (one)	Austria/women/47 years	House dust mite	Rhinitis	Six years after end of SIT. Aluminium particles detected in granulomas in biopsies of skin outside injection sites

SIT, allergen-specific immunotherapy.

Vasculitis was also the type of reaction that was most commonly reported as being reproducible on repeated exposure to SIT. The mechanisms underlying vasculitis reactions are likely to be a type 3 immune reaction with circulating immune complexes. Consistent with this, evidence of circulating immune complexes was detected in some of the cases [10,12,16]. In contrast, earlier biochemical investigations of patients treated with SIT could not detect evidence of immune complexes following SIT [19–23]. One may argue that formation of immune complexes following injection of allergens is not an autoimmune reaction *per se*, although the resulting pathological reaction (vasculitis) is similar to that of some autoimmune diseases. It may be speculated that risk of immune complexes could be higher following injection of mixtures of allergens or less purified allergen extracts.

Whether the number of reported cases observed in relation to SIT is higher or lower than what would be expected by chance is not possible to determine. The number seems low considering that SIT has been used for 100 years and that patients are usually treated for years. On the contrary, it is likely that not all cases of autoimmune disease with potential relation to SIT have been published and the reported cases likely represent an underestimate of the true number of incident cases of autoimmune disease occurring in patients treated with SIT. However, this argument also relates to other types of allergy treatment, and only data from properly controlled studies, in particular randomized studies can provide unbiased estimates as discussed above.

It is beyond the scope of this review to describe the possible mechanisms underlying a potential link between SIT and autoimmune diseases. In the above reported cases, the allergen extracts were, with one exception (venom extract), inhalant allergens and in particular mixtures of inhalant allergens. It should be noted that the immunological effects of both allergens and adjuvant used to increase the immune response could be responsible for any potential effects of SIT on the immune system. Also, due to improved purification and standardization techniques commercially available allergen extracts have changed markedly over the years, not necessarily reflecting the extracts used before.

CONCLUSION

Evidence to support the idea that SIT can act as a trigger of autoimmune diseases is weak and mainly based on case reports and speculations about biological plausibility. Vasculitis reactions accounted for the majority of case reports retrieved in our literature search. Whether the number of reported

cases observed in relation to SIT is higher or lower than what would be expected by chance is not possible to determine from existing data. The number of reported cases should be viewed in the light of the fact that SIT is often given to patients for years and that SIT has been used as a treatment for allergy for 100 years. There are no published data on autoimmune disease development in patients participating in randomized trials of the effects of SIT. One nonrandomized pharmacoepidemiological study failed to detect any increased risk of autoimmune disease development during SIT as compared with the risk during conventional allergy treatment.

From a clinical perspective, the risk of autoimmune disease in patients receiving SIT is very low. It has not been possible to determine whether the risk is comparable to the risk in patients receiving other types of allergy treatment. A few cases of autoimmune disease, mainly vasculitis, development with highly plausible relation to SIT have been published. It is reasonable to recommend that SIT is discontinued in the event of any potential sign/symptom of autoimmune disease and the patient carefully examined including evaluation of the possible relation between SIT and symptoms. Furthermore, as a principle of caution, it seems reasonable to carefully evaluate the indication for SIT, that is risks versus benefits, in patients with established autoimmune disease or a strong family history of autoimmune disease.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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